Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Repurposing antimalarials and other drugs for COVID-19

The COVID-19 pandemic, caused by the coronavirus SARS-CoV-2, now affects countries on six continents. Reported case numbers are certainly underestimates given the low rates of testing in many countries, a virus with a basic reproductive value (R_0) of apparently over 2.2, and evidence of viral shedding from asymptomatic infected people [1]. Social distancing, hand hygiene and community mitigation measures are recommended to contain this pandemic [2]. These measures aim at 'flattening the curve' of the initial wave of infections ripping through the various countries and regions, leading to an acute overburdening of health care services. Even if in part successful, many researchers are predicting a "new wave" of COVID-19 infections. Whilst massive efforts are underway to change this, there is currently no vaccine, no prophylaxis, few proposed specific treatments and there are to date, naturally, few data on the sequelae or longer-term outcomes of the infection. It is unknown whether or not those second waves will occur and if they do, will they occur in persons who have already been exposed to the SARS-CoV-2 virus or in naïve persons? All forecasts regarding herd immunity remain speculations. Countries, such as China, that have passed the epidemic peak are now importing fresh cases from countries more recently affected. For health care workers (HCW) on the frontline and for patients with severe illness, the urgent search for a treatment is on. Until a vaccine is available, it would also be valuable to have an option for prophylaxis of HCW enabling the protection of those on the frontline. Furthermore, a therapy would expedite viral load reduction and allow HCW to return to work faster. The need for a treatment is particularly urgent, as a therapy could reduce the time spent in intensive care units and free up beds. A candidate therapy could be a single drug or substance or a combination and these candidates should preferably be repurposed drugs.

Some new papers have reported on therapy options. A Chinese team published results of a study demonstrating that chloroquine, an antimalarial, and its hydroxyl analogue, hydroxychloroquine, inhibit SARS-CoV-2 *in vitro* with hydroxychloroquine (EC50 = 0.72%μM) found to be more potent than chloroquine (EC50 = 5.47%μM) [3]. A French paper reporting on the use of drug combinations in infected patients highlighted the possibility that hydroxychloroquine is effective in the treatment of COVID-19 patients [4] particularly in combination with azithromycin. In this study, with a limited number of patients, hydroxychloroquine with azithromycin was shown to clear viral nasopharyngeal carriage of SARS-CoV-2 in just three to six days. These results are important because a recent paper has shown that the mean duration of viral shedding in patients suffering from COVID-19 in China was up to 20 days and even 37 days for the longest duration [5].

Antimalarials are potential candidates to be "repurposed" as they have been widely studied and evaluated in both the therapy and prophylaxis settings. Furthermore, they have been used in a broad range of age groups and in persons with co-morbidities. There is a body of evidence available regarding drug/drug interactions, metabolic pathways, pharmacokinetics, posology and galenics. Formulations are available that would suit both ambulatory and stationary settings. These include tablet forms, rectal formulations and solutions for injection. We have well controlled studies evaluating treatment and the tolerability of chemoprophylaxis [6]. There are a variety of classes of antimalarial medications, including artemisinin derivatives (derived from the plant *Artemisia annua*), quinine and related drugs (such as mefloquine, halofantrine, lumefantrine), aminoquinolines (such as chloroquine, amodiaquine, primaquine) and a mixed group of compounds with formidable antimalarial potential (including doxycycline, atovaquone, sulfonamides). The story of the rediscovery of the sesquiterpene lactone, artemisinin in China, an active principle derived from plants described as "fever reducing" in ancient pharmacopoeia, and repurposing this class as antimalarials is a classical case of using existing treatments for new indications. The World Health Organisation (WHO) can be applauded for the launch of the SOLIDARITY study [7] that will focus on collating robust, clinical evidence on a number of potential COVID-19 therapeutics. Chloroquine and hydroxychloroquine are included in the panel of drugs under investigation.

Apart from antimalarials, some antivirals have also shown promise against the novel coronaviruses: *In vitro* studies have shown that the antiviral remdesivir can inhibit coronaviruses such as SARS-CoV and MERS-CoV [8]. In an *in vitro* test using human airway epithelial cell cultures, remdesivir was effective against other coronaviruses [9]. One study showed that remdesivir and interferon beta were superior to lopinavir, ritonavir and interferon beta both *in vitro* and in a MERS-CoV mouse model. Remdesivir, administered alone or in combination with chloroquine [10] is also considered to be effective and has been used with success. Major multicentre trials to systematically assess its efficacy and safety in moderate and severe COVID-19 disease are currently underway (ClinicalTrials.gov Identifiers: NCT04292899; NCT04292730 and others).

Beside several antivirals and antimalarials, there are other pharmacological classes that must be considered for use against SARS-CoV-2. For instance, teicoplanin was proposed as a potential treatment in COVID-19 patients and has already shown inhibitory effects on cell entry of Ebola virus, SARS-CoV and MERS-CoV in the past. Its *in vitro* activity against SARS-CoV-2 was reported by Zhang et al. [11]. However, it has to be acknowledged that in this and other cases, it is a long, expensive and time-consuming way, even if there is an accelerated avenue to expedite promising developments, from *in vitro* assays indicative of antiviral effects to the initiation steps of safety and efficacy assessments in humans, Finding compounds that can block the entry of the virus into the cell could be an important approach to find potential therapies for COVID-19. Recent research has also examined the mechanism used by SARS-CoV-2 for facilitating cell entry [12]. This cell

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entry seems to be crucial for the virus to infect the cell and uses angiotensin-converting enzyme 2 (ACE2) [12] as well as the transmembrane protease, serine 2 (TMPRSS2), that are both expressed on human cells. This entry was already described in the past for SARS-CoV. SARS-CoV-2 binds with its own spike glycoprotein to ACE2 and uses the serine protease TMPRSS2 for priming. This allows for easier fusion of viral and cellular membranes. ACE2 is expressed in lungs, heart, kidneys and intestine and is known to convert angiotensin II into angiotensin (1-7), thus effecting blood pressure and cardiac function.

An important advantage of reviewing, evaluating and condensing evidence on available molecules, active principles or drugs is that this approach brings important key, existing medical data to the fore. It will not just be enough to have candidate drugs that work *in vitro* against SARS-CoV-2. It is essential that the identified candidate or combination of candidates have a good safety profile, have matching pharmacokinetics and, if possible, different viral targets. If antimalarials can be repurposed for COVID-19, travel and tropical medicine experts can bring their expertise to the table as antimalarials are the "bread and butter" of travel medicine and there is a wealth of experience and knowledge on the use and tolerability of these drugs in all ages and in persons with co-morbidities. It is time to bring this knowledge to a new front in the war on COVID-19.

References

[1] Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W, Seilmaier M, Drosten C, Vollmar P, Zwirglmaier K, Zange S, Wölfel R, Hoelscher M. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020 Mar 5;382(10):970–1. https://doi.org/10.1056/NEJMc2001468.

[2] Ebrahim SH, Ahmed QA, Gozzer E, Schlagenhauf P, Memish ZA. COVID-19 and community mitigation strategies in a pandemic. BMJ 2020 Mar 17;368:m1066. https://doi.org/10.1136/bmj.m1066.

[3] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020 Mar 9. https://doi.org/10.1093/cid/ciaa237. pii: ciaa237.

[4] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 Mar 20:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.

[5] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 11. https://doi.org/10.1016/S0140-6736(20)30566-3. pii: S0140-6736(20)30566-3.

[6] Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, Herold M, Krebs B, Veit O, Allwinn R, Steffen R. Tolerability of malaria chemoprophylaxis in non-immune travellers to Sub-Saharan Africa: a multi-centre, randomised, double-blind, four-arm study. BMJ 2003 Nov 8;327(7423):1078.

[7] WHO SOLIDARITY.

[8] Momattin H, Al-Ali AY, Al-Tawfiq JA. Systematic review of the therapeutic agents for the treatment of the Middle East Respiratory Syndrome Coronavirus (MERS –CoV). Trav Med Infect Dis 2019 Jul - Aug;30:9–18. https://doi.org/10.1016/j.tmaid.2019.06.012. Epub 2019 Jun 25.

[9] Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID_19. Trav Med Infect Dis 2020 Mar 5:101615. https://doi.org/10.1016/j.tmaid.2020.101615.

[10] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020 Mar;30(3):269–71. https://doi.org/10.1038/s41422-020-0282-0.

[11] Zhang J, Ma X, Yu F, Liu J, Zou F, Pan T, Zhang H. Teicoplanin potently blocks the cell entry of 2019-nCoV. bioRxiv 2020.02.05. p. 935387. https://doi.org/10.1101/2020.02.05.935387.

[12] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020 Mar 4. https://doi.org/10.1016/j.cell.2020.02.052. pii: S0092-8674(20)30229-4.

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